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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Woodcock Washburn Kurtz
Mackiewicz & Norris LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103

EXAMINER
MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
1624	8

DATE MAILED: 02/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/899,488	LANGHAM ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21 and 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 1/6/03. Applicants amended claims 1, 12, 15, 19, 21, and 23-26. Claim 22 was canceled. Claim 27 is new. There are twenty-six claims pending and twenty-six under consideration. Claims 1-19 and 27 are compound claims. Claim 20 is a composition claim. Claims 21 and 23-26 are use claims. All pending claims were previously rejected. This is the second action on the merits. The application concerns some cyclobut-3-en-1,2-dione compounds, compositions, and uses thereof.

Information Disclosure Statement

2. The information disclosure statement filed 1/6/03 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

3. The references in appendixes A-E filed 1/6/03 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

Response to Amendment

4. Applicants' amendment listing the specific linker groups they claim overcomes the indefiniteness rejection made in point #2 of the previous office

action. Applicants replacement of derivative by acid bioisostere, coupled with Applicants citation of Wermuth (The Practice of Medicinal Chemistry) as providing the structure of such acid isosteres and the evidence that they are art-recognized as such in medicianl chemistry overcomes the indefiniteness rejection made in points #3 and #4. Applicants' removal of particularly from claim 19 overcomes the indefiniteness rejection made in point #6. The esters and amides they intend are described in lines 20-26, page11. Applicants' listing of the diseases they intend to treat overcomes both the indefiniteness rejection made in point #7 and the enablement rejection made in point #11.

Applicants' cancellation of claim 22 and amendments to claims 22 and 23, correcting a typo in dependency overcomes the indefiniteness rejection made in point #8. Applicants' deletion of "prophylaxis from claim 21 overcomes the enablement rejection made in point #10. Applicants amendment to claims 25 and 26, stating that their compounds are intended only for sick people overcomes the enablement rejection made in point #13 but has triggered a new indefiniteness rejection.

Claim Rejections - 35 USC § 112

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-12, 14-18, 20, 21, and 23-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention. The words, in the definition of R2 spanning pages 3-4 of the recent amendment "heteocycloalkyl", "heteocycloalkenyl", "bicycloheteroalkyl", "bicycloheteroalkenyl", "tricycloheteroalkyl", and "tricycloheteroalkenyl", are indefinite. Firstly, while applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). There is no such thing. Is "heteocycloalkyl" an alkyl substituted by a heterocycle, e.g. pyridyl-methyl? A cycloalkyl interrupted by a heteroatom, such as piperidinyl? A cycloalkyl substituted by a heteroatom, e.g. methoxycyclopropyl? Whatever choice is selected must be supported by the specification. Applicants do not define any of these terms in the specification. The definition of cycloalkyl, which Applicants provide in lines 1-7, page 9 does not include the possibility of hetero atoms inserted into the carbon ring but does not distinguish between the other two possibilities. Furthermore, in lines 9-15, page 9 Applicants offer piperidinyl as an example of a "heterocyclic ring", implying that a "heterocycloalkyl" must be something different.

Applicants have replaced " heterocycloaliphatic" with "heterocycloalkyl" and point to lines 25-28, page 15 in support of their amendment. This passage

presumably clarifies their intended meaning. This is not persuasive. The passage cited informs us that the ring may "contain" a heteroatom. Does contain mean in the ring or on the ring? Which heteroatoms? In the previous action, the Examiner asked some specific questions concerning the meaning of "heterocycloaliphatic" which also pertain to "heterocycloalkyl". If Applicants cannot answer the questions, then how is the public to understand the metes and bounds of the claims?

6. Claims 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "a disease or disorder associated with elevated a_4 integrin activity *** to the ligands thereof". It is unclear what diseases and treatments applicant is intending to encompass. The paragraph spanning pages 1-2 and the following paragraph list some intergin associated diseases but appear to have nothing to do with α_4. Similarly, the last paragraph on page 3 states that number of diseases might benefit from treatment but fails to state what those diseases are. The passage spanning line 31, page 28 to line 5, page 29 lists the diseases Applicants intend to treat but do not state the diseases are associated with elevated a_4 integrin activity. Identifying which

diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

7. Claims 1-21, 23-26 remain rejected and claim 27 is newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the salts and N-oxides of the claimed compounds, does not reasonably provide enablement for making "solvates" or "hydrates" of the claimed compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. There are two grounds for making this rejection. Firstly, what solvents are contemplated for making the "solvates"?

Secondly, the claims are drawn to solvates and hydrates. However, all the compounds presented in the nine examples spanning pages 42-45 all failed to produce a solvate or hydrate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not

produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly. It is unpredictable whether a particular solvent or water will form a solvate or hydrate with a particular host molecule. The Examiner suggests deleting the two words.

Applicants cite Haack's definition of solvate and hydrate and urge that this demonstrates that undue experimentation is not required to prepare these compounds. This is not persuasive because the issue is not indefiniteness concerning the concept of solvate but Applicants' direction for the preparation of a solvate and the lack of predictability in this art.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims." *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. Determining if any particular substrate would form a hydrate or

solvate would require synthesis of the substrate and subjecting it to recrystallization with water and a variety of solvents. This must be done at a variety of different temperatures and pressures because any particular hydrate or solvate is stable only over a limited range of conditions. The crystal formed would have to be characterized to determine if a hydrate or solvate had formed and what its composition was. This is a moderate degree of experimentation.

There is no direction in the specification concerning how to make any hydrate or solvate. The lack of working examples was discussed above. The nature of the invention is in the arts of medicinal chemistry and physical pharmacy. The state of the art is summarized in the annual report of 1999 of University of Minnesota--Twin Cities Campus College of Pharmacy found at http://www.msi.umn.edu/general/Reports/ar99/departments/pharmacy.html

David J.W. Grant, writes, "Crystal Structures and Molecular Simulations Sulfonamides comprise a class of widely used antibacterial drugs. The crystal structures of various polymorphic phases have been solved and published. However, little work has focused on their solvates. In this laboratory, four sulfonamides (sulfapyridine, sulfadiazine, sulfamerazine, and sulfamethazine) were examined, and over a dozen solvates were discovered. The structures of these solvates are now being determined. The objectives of this study are to probe the

intermolecular interactions between the drug and solvent in each solvate and to compare the crystal structures of the solvates with those of the parent drugs and among the solvates themselves. Ultimately, this group is gaining an understanding of how the solvent affects the properties of the drug and the reason behind the formation of each solvate. The researchers are working to predict solvate formation based on the structure of the drug."

The sulfonamide drugs discussed above are over fifty years old. Yet in 1999 the neither synthesis nor the structure of such solvates was not known for even such a well-studied class of molecules.

The artisan making Applicants' invention would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. The predictability in this art is taught by West (Solid State Chemistry) as non-existent in 1988. Grant reports that in 1999 that "researchers are working to predict solvate formation based on the structure of the drug." But presumably had not succeed in that endeavor by 1999.

Joachim Ulrich, (Kirk-Othmer Encyclopedia of Chemical Technology) writes, "Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities,

solubilities, dissolution rates, colors, hardnesses, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stabile region of the pseudopolymorph." Thus, both synthesis and prediction of the structure of such hydrates and solvates are less certain arts that synthesis and structure prediction of other polymorphs.

In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced.

In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent." Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the absence of any teaching in the specification of how to form any solvate of Applicants' compounds, undue experimentation will be required.

8. Claim 21 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the other listed diseases of claim 22, does not reasonably provide enablement for treating multiple sclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Polman (BMJ) reports in the table on page 492 that interferon is the only established therapy for multiple sclerosis. Glatiramer acetate is a second line treatment used in the US but not Europe. Cohen (J. Neuroimmun.) in Table 3 on page 30 states that the only available treatment options for multiple sclerosis are interferon (rlFNβ), Glatiramer acetate (GA), the steroid methylprednisolone (IVMP), the immunesuppresives azathioprine (AZA), methotrexate (MTX), and cyclophosphamide (CTX), and immunglobin (IVIg). Cell adhesion inhibitors are not presently art-recognized to be efficacious for this purpose. Thus, the skilled clinician would not know how to use them to treat MS with Applicants' compounds. Case law is clear on this point. In an unpredictable art, such as MS therapy, models may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy.

Applicants cite the "Drug Report" concerning clinical trials of the antibody, ANTEGREN in MS. ANTEGREN is a monoclonal humanized antibody against

the integrin $\alpha_4\beta_1$. This is not persuasive for three reasons. Firstly, the results of the phase II trial, which would be the first indication of efficacy against MS disease, were not available until September 2001 well after Applicants' effective filing date in 2000. Secondly, Applicants describe in the first two paragraphs on page 46 a method of performing an integrin $\alpha_4\beta_1$ assay but present no data. How is the potency of ANTEGREN in this assay to be compared that that of Applicants' compounds? Thirdly, what is the correlation between the assay described and clinical efficacy in MS treatment? What potency in Applicants' assay is art-recognized as indicative of clinical efficacy? Presumably ANTEGREN is active but how many false positives are found by this assay?

Double Patenting

9. Claims 1-14, 20, 21, and 23-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims1-6, 10-15, and 18-22 of U.S. Patent No. 6,518,283. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of U.S. Patent No. 6,518,283 claims the "Het" of the present application as Ar^1, which is "naphthyridinyl" generally. Applicants' provisos in the last three lines of the present claim 1 exclude two specific naphthyridinyl rings with two specific

attachment points. There are other naphthyridinyl rings and other attachment points not excluded by this proviso.

According to the MPEP §806.04(i) "Generic Claims Presented for First Time After Issue of Species. The Office no longer follows the practice of prohibiting the allowance of generic claims that are presented for the first time after the issuance of a copending application claiming plural species. Instead, the Office may reject the generic claims on the grounds of obviousness-type double patenting. Applicant may overcome such a rejection by filing a terminal disclaimer. See *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29."

10. Claims 1-21 and 23-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14, and 18 of U.S. Patent No. 6.455.539. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of U.S. Patent No. 6.455.539 claims the "Het" of the present application as Ar^1, which is "a heteroaromatic group" generally, which would include the fused ring heteroaromatic group of the present application.

Conclusion

11. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final

amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK
February 12, 2003